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SAFETY AND EFFECTIVENESS OF INSULIN DETEMIR IN COMBINATION WITH ORAL ANTIDIABETIC AGENTS IN AN OUTPATIENT SPECIALIST SETTING: RESULTS OF THE ITALIAN SOLVE™ OBSERVATIONAL STUDY

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on behalf of the Italian SOLVE™ Study Group

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Safety and effectiveness of insulin detemir in combination with oral antidiabetic agents in an outpatient specialist setting: results of the Italian SOLVE™ observational study

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Aim. **The addition of basal insulin to oral antidiabetics (OADs) is described by a large number of guidelines and commonly used in clinical practice as a way to start insulin therapy in patient with type 2 diabetes mellitus in order to maximize compliance and minimise the impact of side effects (mainly hypoglycaemia and body weight increase).**

Methods. **SOLVE™ was a 24-weeks international observational study conducted in 10 countries (including Italy) for the evaluation of the safety and effectiveness of once-daily insulin detemir as add-on therapy in people with type 2 diabetes mellitus (T2DM) already treated with one or more OADs. The Italian arm of the Solve™ Study aimed to evaluate the safety and the effectiveness of once-daily insulin detemir in combination with OADs agents for the treatment of patients with T2DM in the Italian outpatient specialist setting. The primary endpoint was to assess the incidence of serious adverse drug reactions (SADRs) including in the specific major hypoglycaemic events during 24 weeks of once-daily insulin detemir treatment.**

Results. **A total of 4625 patients were enrolled in the study by 223 Italian centres for diabetes care. At baseline the mean (±SD) demographic characteristics of the patientswere: age 66.5 (±10.0) years, duration of diabetes 13.25 (±8.14) years, weight 78.95 (±15.86) kg and BMI 29.5 kg/m² (±5.0). At the end of the study, 3 SADRs (of which 2 major hypoglycemia) were reported in 2 patients (<0.1%). The percentage of patients with at least 1 minor hypoglycemic event during the 4 weeks preceding insulin initiation was 3.6%. Following insulin initiation, 5.7% (as recorded at baseline visit) at least 1 minor hypoglycemic event, wich decreased slightly by the end of the study compared to baseline (4.8%). In addition, before insulin initiation the (±SD) glycemic control values were: fasting plasma glucose (FPG) 11.43 (±3.2) mmol/L and HbA_{1c} 9.16% (±1.46). At the end of the study, HbA_{1c} was reduced by 1.35% (±1.57) (P<0.001), FPG was reduced by 3.34 mmol/L (P<0.001) and the percentage of patients (with HbA_{1c}<7%) was 21.9%. A mean reduction of 0.52 kg of body weight (P<0.001) was observed compared to before insulin initiation; the body weight reduction was more pronounced in patients with higher BMI before insulin initiation (-1,0 kg for 30<BMI<35; -2,1 kg for BMI<35).**

Conclusion. **In the Italian outpatient setting, once-daily insulin detemir as add-on therapy to OADs was associated with a favourable tolerability profile. The improvement of the glycaemic control after insulin initiation with insulin detemir was clinically significant and did not cause an increase in body weight or hypoglycaemia.**

KEY WORDS: Insulin - Blood glucose - Clinical protocols.

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Maintaining adequate metabolic control remains a challenge in many patients with type 2 diabetes (T2DM).[1] Recent trials confirmed the existence of a "metabolic memory", strongly supporting the adoption of an early, aggressive treat-to-target approach, instead of waiting for treatment failure.[2] This approach can be particularly important in the early stages of the disease, to slow down the progressive decline of β-cell function and improve overall outcomes.[3] Nevertheless, data from 114.000 patients in Italy suggest that over 50% of them fail to meet the HbA_{1c} target of <7.0%, while approximately 30% have HbA_{1c} levels above 8.0%.[4]

Among the many factors proposed to explain the failure to achieve recommended goals, clinical inertia is increasingly recognized as a primary cause of poor glycemic control.[5] Clinical inertia in T2DM has been confirmed in several studies showing that patients remain in a state of chronic hyperglycemia for long periods of time before treatment is intensified.[1, 5] Basal insulin is recommended as one of the second line therapies after metformin as reported in the recent ADA/EASD Position Statement.[6]

However, in spite of the results of numerous clinical trials demonstrating the efficacy and safety of adding basal insulin to oral antidiabetic drugs (OADs),[8, 9] insulin therapy is often initiated only after many years of poor glycemic control.[10] The risk of hypoglycemia and weight gain are still as the main causes for the delay of insulin therapy initiation and intensification.[11]

Among the available basal insulins, the use of analogues has been associated with a lower risk of hypoglycemia compared to NPH insulin.[12-14] In addition, between the basal analogues, insulin detemir has a more favorable effect on body weight compared to insulin glargine.[15]

Besides randomiZed clinical trials, important complementary data on effectiveness and safety of insulin analogues can be derived from observational studies, to evaluate effectiveness, tolerability and manageability of treatment in a real-world setting.[16]

Given these premises, the SOLVE™ (Study of Once-daily Levemir®) observational study has been designed to assess safety and effectiveness of insulin detemir initiation in individuals with type 2 diabetes mellitus (T2DM) poorly controlled with OAD therapy under routine clinical practice conditions.

The project involved both general practitioners and specialists in 2817 centres in 10 countries and included a total of 17,374 patients.[17, 18] The article focus on the results of the Italian sub-population.

Materials and methods

The Italian SOLVE™ Study involved 233 diabetes outpatient clinics. Patients were enrolled into the study at the discretion of the Investigators, following the therapeutic decision to initiate once-daily insulin detemir.

The inclusion criteria were: age ≥18 years, diagnosis of T2DM, current treatment with once daily insulin detemir in combination with one or more OADs, HbA_{1c} levels above the established target and signed informed consent.

The exclusion criteria were: known or suspected allergy to insulin detemir or any of its excipients, pregnancy/lactation/intention to become pregnant within the next 6 months, patient not using contraceptive methods.

The withdrawal criteria were: change in insulin detemir dosing from once-daily during the study, pregnancy and intention to become pregnant, withdrawal of informed consent.

Data were collected at 4 time points: preinsulin (last visit before insulin detemir initiation), baseline (day of inclusion in the study), and 12 and 24 weeks. The data were selected among those available from the routine visits closest to the scheduled study protocol visit. Patients were followed-up for 24 weeks. During the follow-up period the dose of insulin detemir and its titration were patient-specific and managed by the physician according to the local care practices. No additional specific treatment recommendations were provided during the study.

The primary endpoint was the incidence of serious adverse drug reactions (SADRs) during 24 weeks of once daily insulin detemir treatment. Episodes of major hypoglycemia were included in the definition of SADR.

Secondary end-points included:

— incidence of all adverse drug reactions (ADRs);

— incidence of major hypoglycemic events (as defined below) and incidence of minor hypoglycaemic events in the 4 weeks preceding the baseline, and a defined period before 12° and 24° week visits;

— HbA_{1c} and its change from baseline after 12 and 24 weeks;

— FPG and its change from baseline after 12 and 24 weeks;

— FPG variability (measured as standard deviation of FPG) and its change from

— baseline at the 12 and 24 weeks visits;

— body weight and its change from baseline at 12- and 24-week visits;

proportion of patients achieving HbA_{1c}<7.0% or HbA_{1c}<6.5% at end of study.

An hypoglycemic episode was defined as major if the subject was not able to treat the episode him/herself and if food, glucagon or i.v. glucose needed to be administrated to the subject by another person due to severe central nervous system (CNS) dysfunction. All the major episodes occurred in the 12 weeks preceding the baseline, 12 and 24 week visits were recorded based on patients' self-reporting.

Minor hypoglycemia was defined as a blood glucose measurement of <3.1 mmol/L with or without symptoms, self-reported by the patients in the last 4 weeks prior to each visit.

Statistical analysis

All patients with at least one administration of insulin detemir and with at least one report of data on safety were included in the Full Analysis Set (FAS).

All patients from the FAS with at least one measurement (from preinsulin to final visit) concerning FPG, HbA_{1c}, weight or hypoglycemic events (yes, no) and a follow-up time of at least 16 to not more than 32 weeks have been included in the Effectiveness Analysis Set (EAS).

The analyses of baseline characteristics and safety data were performed on FAS and the analyses of the efficacy outcome variables were performed on EAS.

Statistical testing/comparison of data before and after initiation of insulin detemir therapy were performed with paired *t*-tests for continuous variables such as weight, HbA_{1c}, or mean FPG, with Wilcoxon test for ordinal categorical variables and with McNemar test for discrete variables such as incidence of hypoglycemic events.

The incidence of hypoglycemia was expressed as number of events per patient/year and percentage of patients reporting the event.

All testing were based on two-sided tests with the criteria set at α=0.05; all results were interpreted in a descriptive manner; missing data have not be replaced.

Results

Patients' characteristics

The Italian SOLVE™ study involved 223 centres. Overall, 4625 patients were included in the FAS, while 3864 patients were included in the EAS (Figure 1). The study was completed by 3996 (86.4%) individuals, while 628 patients (13.6%) discontinued the study. The main reasons for premature study withdrawal were: patients lost to follow-up (4.1%), discontinuation of insulin detemir (1.5%), need for additional daily administrations of insulin detemir (0.9%), interruption of OAD (0.9%), addition of short-acting insulin (3.4%), ADR (0.02%), and other (2.9%).

A summary of patients' characteristics (FAS population) is reported in Table I.

Patients had been diagnosed with T2DM for a mean of 13.25 years (SD: 8.14; N.=4615) and had been on OAD therapy for a mean of 11.43 years (SD: 7.49; N.=4531). Macrovascular complications were present in 30.5% (N.=1386/4545) of patients and microvascu-

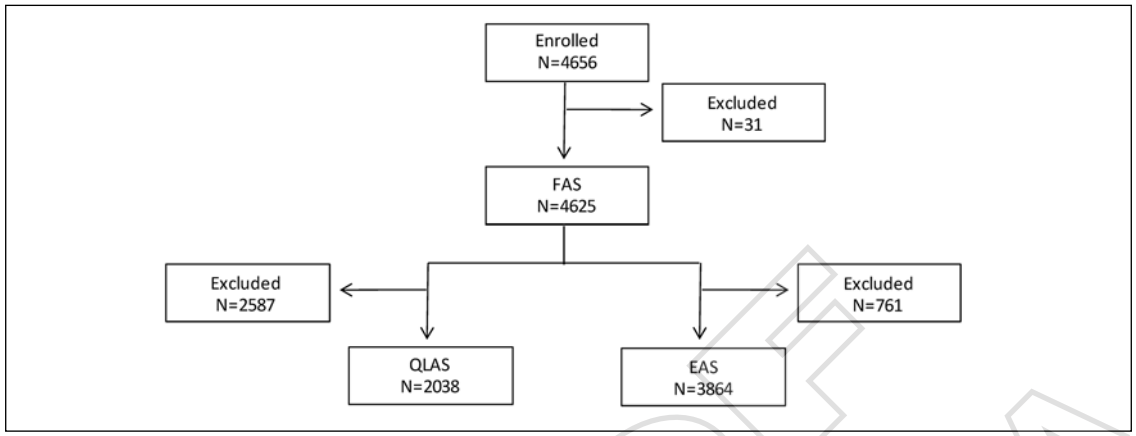


Figure 1.—Disposition of patients.

TABLE I.—*Demographic and patients' characteristics at the baseline (BMI and complicances are subcategories).*

Age (years, mean±SD)	66.5±10.0
% of patient aged ≤65 years	40.4
% of patient aged >65 years	59.6
Males (%)	52.7
Diabetes duration (years, mean±SD)	13.25±8.14
OHA therapy duration (years, mean±SD)	11.43±7.49
Macro-vascular complications (%)	30.5
Micro-vascular complications (%)	37.8
History of acute myocardial infarction (%)	11.5
Neuropathy (%)	14.4
Retinopathy (%)	22.5
Nephropathy (%)	12.8
HbA_{1c} (%)	9.16±1.46
HbA_{1c}>9.0% (%)	50.1
BMI (kg/m², mean±SD)	29.45±5.05
% of patient with BMI≤25 kg/m²	18.5
% of patient with BMI>25 and ≤30 kg/m²	40.3
% of patient with BMI>30 kg/m²	41.2

lar complications in 37.8% (N.=1720/4547) of patients.

Overall, 11.5% (N.=531/4608) of patients had history of myocardial infarction, 7.9% (N.=363/4608) of angina pectoris, 14.4% (N.=664/4608) of neuropathy, 22.5% (N.=1038/4608) of retinopathy, 12.8% (N.=592/4608) of nephropathy, 4.1% (N.=191/4608) of cardiovascular accident, 3.3% (N.=151/4608) of transient ischemic attack, 4.6% (N.=214/4608) of coronary artery bypass graft, 7.7% (N.=356/4608) of angioplasty, and 12.9% (N.=593/4608) of peripheral vascular disease.

At baseline, 85.4% (N.=3899/4567) of patients were on biguanides either alone or combined with other OADs, 68.6% (N.=3131/4567) on sulphonylureas, 20.9% (N.=954/4567) on glinides, 11.2% (N.=512/4567) on thiazolidinediones, 4.8% (N.=218/4567) on α-glucosidase inhibitors, and 1.5% (N.=69/4567) on DPP-IV (dipeptidyl peptidase IV) inhibitors. At insulin initiation, biguanides were prescribed to 81.8% (N.=3773/4614) of patients, sulphonylureas to 59.6% (N.=2750/4614), glinides to 26.7% (N.=1231/4614), thiazolidinediones to 6.3% (N.=291/4614), α-glucosidase-inhibitors to 3.6% (N.=164/4614), and DPP-IV inhibitors to 0.5% (N.=22/4614). At baseline, interim and final visits the proportion of patients prescribed with each

OAD remained similar to that prescribed at insulin initiation.

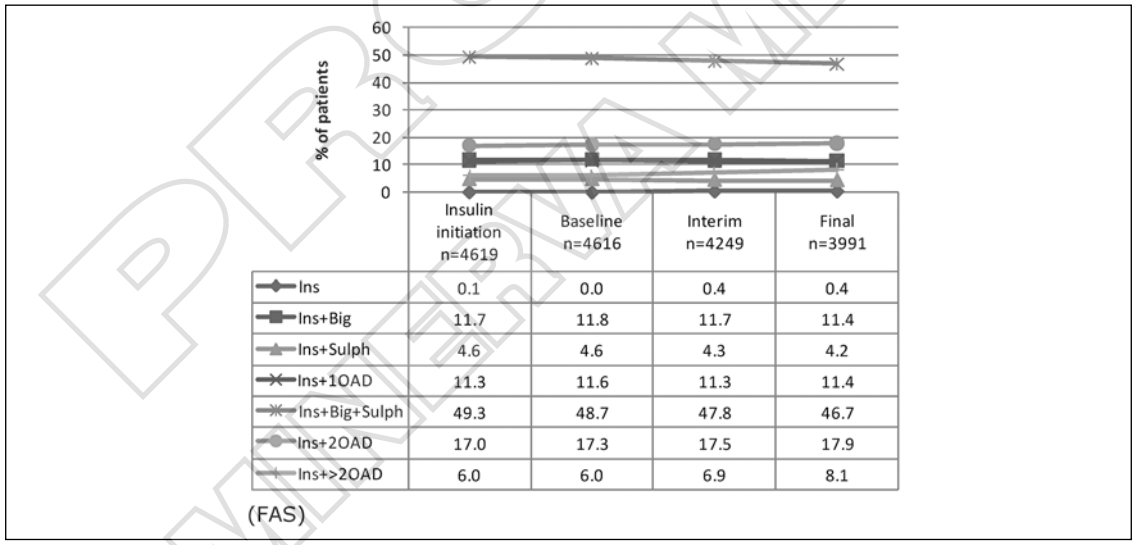
At insulin initiation as well as at baseline, interim and final visit the two most frequently insulin regimens were insulin with biguanides and sulphonylureas (initiation: N.=2275/4619, 49.3%; baseline: N.=2246/4616, 48.7%; interim: N.=2033/4249, 47.8%; final: N.=1862/3991, 46.7%), and insulin with 2 OADs excluding biguanides and sulphonylureas (initiation: N.=783/4619, 17.0%; baseline: N.=797/4616, 17.3%; interim: N.=744/4249, 17.5%; final: N.=716/3991, 17.9%) (Figure 2). The number of concomitant OAD per patient did not change significantly before (1.9) and after basal (1.8) insulin initiation (Table II).

Safety

The primary endpoint of this study was the incidence of SADRs, including major hypoglycaemic events during the 24 weeks of treatment with once-daily insulin detemir. Overall, 3 SADRs occurred during the study and were reported by 2 patients (0.05%), including 2 severe hypoglycemic episodes that were considered as possibly related to insulin detemir and occurred following a skipped meal.

The proportion of patients reporting to have experienced at least one minor hypoglycaemic event during the 4 weeks preceding insulin initiation was 3.6% (N.=166/4621), while it was 5.7% (N.=265/4624), 5.2% (N.=224/4282) and 4.8% (N.=196/4058) during the 4 weeks before baseline, interim and final visits, respectively.

The incidence of minor hypoglycemic events prior to insulin treatment initiation was 1.232 (N.=4580) events per patient-year, of which 1.045 (N.=4567) and 0.191 (N.=4562) were minor daytime and minor nocturnal events per patient-year respec-



	Insulin initiation n=4619	Baseline n=4616	Interim n=4249	Final n=3991
Ins	0.1	0.0	0.4	0.4
Ins+Big	11.7	11.8	11.7	11.4
Ins+Sulph	4.6	4.6	4.3	4.2
Ins+1OAD	11.3	11.6	11.3	11.4
Ins+Big+Sulph	49.3	48.7	47.8	46.7
Ins+2OAD	17.0	17.3	17.5	17.9
Ins+>2OAD	6.0	6.0	6.9	8.1

Figure 2.—Insulin-based regimen prescribed at insulin initiation and at baseline, interim and final visits.

TABLE II.—*Changes in the prescription of OADs before and after the initiation of insulin detemir.*

	Preinsulin phase (%)	Insulin initiation (%)
Number of drugs (mean+SD)	1.9±0.58	1.8±0.54
% of patients with:		
1 OAD	20.6	27.1
2 OADs	66.8	64.8
>2 OADs	12.6	6.1

tively. During the 4 weeks prior to the interim visit, there were 1.508 (N.=4276) minor events per patient-year, comprising 1.330 (N.=4272) minor daytime events and 0.180 (N.=4254) minor nocturnal events per patient-year. During the 4 weeks prior to the final visit, 1.155 (N.=4053) overall minor events, 0.996 (N.=4046) minor daytime events and 0.162 (N.=4018) minor nocturnal events per patient-year were observed.

The incidence of overall and daytime minor events increased significantly between preinsulin and interim visit assessments (P<0.001). No other significant changes were observed during the study period in the incidence of overall, daytime or nocturnal minor events.

Insulin detemir use and effectiveness in a real life clinical setting

The most frequent time of insulin administration was at bedtime (insulin initiation: N.=3866/4619; 83.7%; baseline visit: N.=3822/4620; 82.7%; interim visit: N.=3510/4271; 82.2%; final visit: N.=3315/4034; 82.2%). The proportion of patients self-administering insulin before breakfast was 9.6% (N.=444/4619) at insulin initiation, 10.5% (N.=487/4620) at baseline visit, 11.1% (N.=475/4271) at interim visit, and 10.6% (N.=426/4034) at the final visit. The proportion of patients self-administering insulin before dinner was 6.6% at insulin initiation (N.=305/4619) and at baseline visit (N.=305/4620), 6.4% (N.=274/4271) at interim visit, and 6.8% (N.=274/4034) at final visit.

The percentage of patients who had the insulin dose changed between baseline and interim visits was 41.6% (N.=1783/4283). At the final visit, the percentage of patients having undergone at least 1 insulin dose change since the interim visit was 32.5% (N.=1320/4058).

The mean dose of insulin prescribed to the overall FAS cohort was 12.33U (SD: 5.68; N.=4619) at insulin initiation, 15.34 units (SD: 7.47; N.=4620) at baseline visit, 17.08 units (SD: 8.47; N.=4269) at interim visit and 18.06 units (SD: 9.12; N.=4035) at the final visit. These doses corresponded to 0.16 units/kg (SD: 0.08; N.=4566), 0.20 units/kg (SD: 0.10; N.=4558), 0.22 units/kg (SD: 0.11; N.=4249), and 0.23 units/kg (SD: 0.12; N.=4024) at insulin initiation, and at baseline, interim and final visits, respectively.

The mean rate of HbA_{1c} for the overall EAS cohort was 9.16% (SD: 1.46; N.=2842) prior to insulin initiation, 8.23% (SD: 1.29; N.=2581) at baseline visit, 7.93% (SD: 1.16; N.=3212) at interim visit and 7.77% (SD: 1.15; N.=3386) at final visit (Table III). For those patients with data on HbA_{1c} concentration at pre-insulin assessment and at final visit, the mean value was 9.16% (SD: 1.44; N.=2572) at pre-insulin measurement, 7.95% (SD: 1.15; N.=2259) at interim visit and 7.81% (SD: 1.14; N.=2572) at the final visit. The mean HbA_{1c} decrease between the assessment prior to insulin initiation and the final visit was statistically significant (change: -1.35%; SD: 1.57; N.=2572; P<0.001) (Table III).

Prior to insulin initiation, 1.3% (N.=38/2842) of patients had their HbA_{1c} level ≤6.5%, 8.0% (N.=227/2842) of patients between 6.5% and ≤7.5% and 90.7% (N.=2577/2842) had a level >7.5%. At final visit, 11.9% (N.=404/3386) of patients had their HbA_{1c} level ≤6.5%, 35.2% (N.=1192/3386) of patients between 6.5% and ≤7.5% and 52.9% (N.=1790/3386) had a level >7.5% (a detailed representation of the patients' distribution by HbA_{1c} value is reported in Figure 3). Overall, prior to insulin initiation 49.9% (N.=1418/2842) of patients had an HbA_{1c} level <9% and 50.1% (N.=1424/2842) ≥9%. At final visit, 85.9% (N.=2907/3386) of patients had an HbA_{1c} level <9% and 14.1% (N.=479/3386) ≥9%.

TABLE III.—*Effectiveness of once daily insulin detemir in combination with OADs under routine clinical practice conditions.*

	Preinsulin	Baseline	Final	Change	
HbA_{1c} (%)(mean±SD)	9.16±1.46	8.23±1.29	7.77±1.15	-1.35±1.57	P<0.001
FPG (mmol/L)(mean±SD)	11.43±3.02	-	7.47±1.82	-3.84±3.30	P<0.001
Body weight (Kg)(mean±SD)	78.95±15.86	78.49±15.41	78.38±15.00	-0.52±5.5	P<0.001

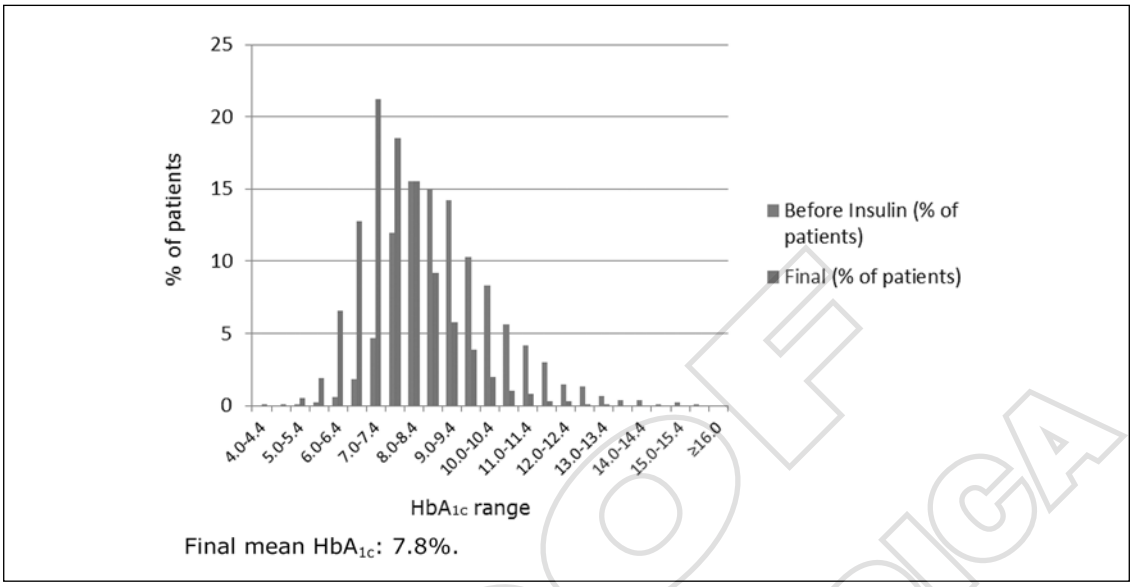


Figure 3.—HbA_{1c} distribution at final visit.

The mean FPG was 11.43 mmol/L (SD: 3.02; N.=856) before insulin initiation, 7.62 mmol/L (SD: 1.89; N.=2405) at interim visit and 7.47 mmol/L (SD: 1.82; N.=2365) at final visit (Table III). For patients with data on FPG prior to insulin initiation and at interim or final visit, the FPG level decreased significantly at the interim visit (change: -3.78 mmol/L; SD: 3.16; N.=733; P<0.001), and at the final visit (change: -3.84 mmol/L; SD: 3.30; N.=722; P<0.001) (Table III).

The mean variability between the three more recent FPG measurements was 2.58 mmol/L (SD: 5.19; N.=535) prior to insulin treatment initiation, 1.29 mmol/L (SD: 2.57; N.=2088) at interim visit and 1.24 mmol/L (SD: 2.61; N.=2043) at final visit. For patients with data on FPG variability prior to insulin initiation and at interim visit, the mean variability at interim visit had decreased significantly by -1.33 mmol/L (SD: 5.40; N.=446; P<0.001). The mean change in FPG variability between pre-insulin assessment and final visit was also statistically significant (change: -1.26 mmol/L; SD: 6.12; N.=441; P<0.001).

The mean weight (FAS) was 78.95 kg (SD: 15.86; N.=4571) prior to insulin initiation, 78.49 kg (SD: 15.41; N.=4563) at baseline visit, 78.63 kg (SD: 15.20; N.=4276) at interim visit, and 78.38 kg (SD: 15.00; N.=4053) at final visit (Table III). A significant weight change was seen at the interim (change: -0.39 kg; N.=4232; P<0.001) and final visits (change: -0.52 kg; N.=4015; P<0.001) compared to pre-insulin assessment (Table III). The highest the initial BMI, the greater the weight average weight loss observed during the study. The percentage of patients losing more than 1 kg between baseline and the final visit was 17.7% (N.=127/716) of patients with BMI at baseline <25 kg/m^2, 33.8% (N.=535/1584) with BMI of 25 to <30 kg/m^2, 40.9% (N.=444/1085) with BMI of 30 to <35 kg/m^2, and 48.2% (N.=264/548) with BMI ≥35 kg/m^2.

Discussion

The results of the Italian cohort of the Solve™ Study provide evidences of insulin detemir safety and effectiveness profile in an outpatient clinical setting. The high number of patients recruited and followed-up makes the results also particularly valuable for their contribution to the description of the clinical and epidemiological characteristic of Italian type 2 diabetic patients requiring insulin therapy initiation.

In the Italian cohort, the main results of our observation have been:

1) a low incidence and a low proportion of patients experiencing at least 1 minor hypo during the 4 weeks prior to the visit and only 2 episodes of severe hypoglycemia, which were due to a skipped meal;

2) a significant reduction in HbA_{1c} of 1.35% without weight gain.

The incidence rates (1.16 events/year/patient) and the prevalence (4.7%) of minor hypoglycemia episodes during the Italian SOLVE™ Study were significantly lower than those previously reported for patients with T2DM treated with insulin,[25] but were comparable to those seen in other studies on insulin detemir.[26]

A possible limitation of the results presented here is the under-reporting of hypoglycemia (at least for the minor episodes).

The HbA_{1c} reduction observed at the end of the Italian SOLVE™ Study is similar to that seen in a randomized clinical trial (RCT) involving patients with the same baseline mean HbA_{1c} and the same duration of diabetes; indeed in the above mentioned study, after 20 weeks of treatment, the HbA_{1c} reduction ranged between 1.48% and 1.58%.[20] The average HbA_{1c} at the end of the Solve™ Study was 7.8%, and distribution of patients by class of HbA_{1c} showed only 21.9% of the patients below 7% while the majority (52.9%) had a level >7.5%. The proportion of patients reaching the target of HbA_{1c} below 7%-7.5% could possibly be increased by adopting a slightly more aggressive titration. Indeed, despite the initial dosage of insulin detemir (12.4 U, 0.16 U/kg) was in line with the SPC recommendation, the final dosage (18.1 U, 0.23 U/kg) in the Italian cohort of the Solve™ Study was lower in comparison with the final average dosage observed in the international SOLVE™ Study [26] and in comparison with the dosage observed at the end of the abovementioned RCT study (0.4 U/kg).[20] This might indicate the attitude of Italian physicians to be more cautious with titration in their real clinical practice.

The low level of titration is probably not justified by an attempt to counterbalance the excessive risk of hypoglycemia since the prevalence of hypoglycemia and the hypoglycaemia incidence rate reported in the present study are very low. This finding could be partially explained by the minor intervention on the modification of the number oral diabetic agents per patient in Italy (from 1.9 to 1.8) compared to the other countries (*e.g.* in Canada from 2.1 to 1.6) [17] possibly leading to a need of lower doses of insulin due to the frequent combination with sulphanilureas (SU).

The Italian SOLVE ™ Study confirmed the beneficial impact of insulin detemir on body weight with a significant reduction of 0.5 kg at the end of the study. Insulin-mediated weight gain is well known [22] and becomes particularly relevant in patients already overweight or obese, which is a common condition also in the population of the Italian Solve™ Study. Weight gain can further exacerbate insulin resistance, placing an additional burden on pancreatic β-cells, increasing the need for exogenous insulin to maintain glycaemic control.[23] Weight gain is one of the barriers to patients' acceptance of insulin initiation, together with fear of hypoglycaemia, injections and, and reluctance to accommodate the inflexible timing of scheduled insulin doses.[24] The weight neutral effect associated with insulin detemir could therefore be beneficial also for the improvement of patient compliance, especially in case of intensive titration. This concept was not taken into consideration for the treatment of patients involved in the Italian Solve™ Study since the titration of insulin detemir dose was extremely low.

Patients starting on insulin therapy seem to be characterized by a very poor metabolic control, and at a mean age and with diabetes duration even higher than patients recruited in other countries involved in the Solve™ Study.[17, 18] This marked clinical inertia has been recorded despite the fact that the Italian cohort of the Solve™ Study being recruited exclusively from an outpatient specialist setting. Such scenarioes might be affected by the geographically heterogeneous organisation of care in Italy. In addition, a late referral to specialist care can also contribute to clinical inertia. Data from AMD An-

nals [19] showed that over a quarter of patients are first referred to specialist care after a diabetes duration of 5 years, with mean levels of HbA_{1c} of 8.2%, and poor control of the cardiovascular risk factors (Table IV).

Conclusions

In conclusion, Italian patients enrolled in the SOLVE™ Study begin insulin therapy when diabetes is poorly controlled and

TABLE IV.—*Supplementary Information: Italian centres involved in the SOLVE™ Study.*

INVESTIGATOR	LOCATION
Alacevich Marco	Pontedecimo (GE)
Allochis Gabriele	Novara
Allotta Gioacchino	Erice (TP)
Amodeo Antonino	Reggio Calabria
Amore Maria Grazia	Acireale (CT)
Andreani Mauro	Urbino (PU)
Aragiusto Concetta	Arzano (NA)
Arosio Maura	Milano
Auletta Pasquale	Frattamaggiore (NA)
Azzarone Vincenza	Manfredonia (FG)
Baggi Viviana	Lodi
Baggiore Cristiana	Firenze
Bargero Giuseppe	Casale Monferrato (AL)
Barone Maria	Caserta
Basciano Francesco	Erice (TP)
Battilomo Antonella	Bracciano (RM)
Belotti Maria Luisa	Palazzolo (BS)
Cappellini Cristina	Bergamo
Bettoni Mario	Firenze
Bevilacqua Maurizio	Milano
Biasi Chiara	Vallo della Lucania (SA)
Bogazzi Anna	Venaria (TO)
Bonomo Matteo	Milano
Borretta Giorgio	Cuneo
Bottia Amodio	Avellino
Bracaccia Massimo	Terni
Bulzomi Rocco	Roma
Burattin Anna (ex Cantalamessa)	Iseo (BS)
Caggiano Domenico	Salerno
Calzolari Giovanna	Mirandola(MO)
Cammilleri Francesca	Viterbo
Candido Riccardo	Trieste
Capitanata Paolo	Aversa (CE)
Caputo Salvatore	Roma
Carboni Luciano	Cagliari
Carlesi Giovanni Paolo	Novi Ligure (AL)
Carlini Maurizio	Torino
Carretti Corrado	Messina
Casartelli Alberto	Como
Castro Francesco	Cetraro (CS)
Cattaneo Anna	Genova
Cavani Rita	Sassuolo (MO)
Cazzolini Clementina	Crema (CR)
Ciancaglini Roberto	Pescara
Ciavarella Adolfo	Bologna
Cicalò Anna Maria	Nuoro
Cicioni Giovanni	Terni
Cimicchi Maria Cristina	Colorno(PR)
Colonna Loredana	Toritto (BA)
Colosio Walfro	Chiari (BS)
Condorelli Emma	Roma
Contini Pierpaolo	Cagliari
Cordaro Gaspare	Paternò (CT)
Cosi Davide	Lecce
Cotti Luisella	Fino
Crispino Giuseppe	Tropea (VV)
Cuzari Gianfranco	Gaggi (ME)
Damasco Anna Maria	Tivoli (RM)
Daniele Pantaleo	Campi Salentina (LE)
De Berardinis Silvestro	Giulianova (TE)
De Candia Lorenzo	Terlizzi (BA)
De Cata Pasquale	Pavia
De Cesare Teresa	Molfetta (BA)
De Luca Ezechiele	Napoli
Del Prato Stefano	Pisa
Desenzani Paolo	Montichiari (BS)
Di Bartolo Paolo	Ravenna
Di Benedetto Antonino	Messina
Di Berardino Paolo	Atri (TE)
Di Carlo Alberto	Lucca
Di Noi Salvatore	Manduria (TA)
Donegà Paola	Occhiobello(RO)
D'Ugo Ercole	Gissi (CH)
Duratorre Edoardo	Luino (VA)
Falasca Paolo	Frascati (RM)
Finocchiaro Concetta	Catania
Fioretto Paola	Padova
Foglini Paolo	Fermo (AP)
Forlani Gabriele	Bologna
Francesconi Andrea	Bagno a Ripoli (FI)
Franzetti Ivano	Varese
Frugiuele Pierluigi	Cosenza
Gambardella Sergio	Roma
Garofalo Arcangela	Vittoria (Ragusa)
Garzaniti Adriana	Pavia
Gentile Antonello	Frosinone
Ghilardi Giosuè	Clusone (BG)
Gibilras Rocco	Gela (CL)
Gioia Daniela	Palermo
Giorda Carlo	Chieri (TO)
Giovannini Celestino	Reggio Calabria
Gnessi Camillo	Latina
Gravina Giuseppe	San Severo (FG)
Graziuso Massimo	Gallatina (LE)
Guglitti Giacomo	Iglesias (CA)
Guarnieri Gianluigi	Conegliano (TV)
Guberti Antonella	Fidenza(PR)
Iannuzzi Filomena	Luzzi
Insalaco Calogera	Canicatti (AG)
Lagomarsini Patrizia	Feltre (BL)
Lanero Marilena	Acqui Terme (AL)
Leccia Giovanni	Aversa (CE)
Leonardi Gaetano	Giarre (CT)
Leotta Carmelo	Catania
Leotta Sergio	Roma
Lorusso Salvatore	Gravina (BA)
Luciano Antonio	Benevento
Maioli Antonello	Potenza
Malci Francesco	Subiaco (RM)
Mancuso Gerardo	Lamezia Terme (CZ)
Manfrini Silvana	Senigallia (AN)
Mannino Domenico	Reggio Calabria
Maolo Gabriele	Macerata
Marangoni Alberto	Bassano del Grappa
Maremmini Anna Maria	Foligno (PG)
Mariniello Paolino	Napoli
Marino Cecilia	Gubbio (PG)
Marsili Alberto	Firenze
Martina Valentino	Torino
Mascetti Paolo	Como
Massenzo Michelina	Quattromiglia di rende
Massidda Albino	Lanusei (OG)
Mastropasqua Arturo	Garbagnate Milanese (MI)
Mattiuzzo Claudio	Tivoli (RM)
Mazzei Bruno	Cosenza
Mileti Giovanni	Cisternino (BR)
Mollo Francesco	Rovigo
Mongelli Sergio	Bari
Morano Susanna	Roma
Moro Ermanno	Venezia
Napoli Angela	Roma
Nassi Rossella	Sansepolcro (AR)
Negri Carlo	Verona
Nogara Andrea	Chioggia (VE)
Orsenigo Gilberto	Como
Orsi Emanuela	Milano
Ottavio Giampietro	Pisa
Paccagnella Agostino	Treviso
Paciotti Vincenzo	Avezzano (AQ)
Parillo Mario	Caserta
Pascale Lisangela	Bitonto (BA)
Pata Pietro	Messina
Perrelli Andrea	Napoli
Perriello Gabriele	Perugia
Perrone Giovanni	Reggio Calabria
Piergiovanni Fabio	Roma
Pinelli Ignazio	Ragusa (ex Elia)
Pipicelli Giuseppe	Soverato (CZ)
Pipitone Antonino	Adria (RO)
Piva Walter	Iesi (AN)
Poccia Gianfranco	L'Aquila
Porro Alfredo	Rho (MI)
Porzuoli Giuseppe	Maddaloni (CE)
Privitera Filippo	Catania
Putignano Pietro	Monza
Quarto Antonio	Massafra (TA)
Querci Fabrizio	Alzano Lombardo (BG)
Ragonesi Dario Pietro	Milano
Rapisarda Salvatore	Ragusa
Rastelli Emilio	Riccione
Reina Giuseppe	Biancavilla (CT)
Ricci Lucia	Arezzo
Ricciardi Grazia Pia	Latina
Riccio Maria Pia	Reggio calabria
Riccio Michele	Napoli
Richini Donato	Esine (BS)
Rocca Alberto	Milano
Romanazzi Vittoria	Monopoli (BA)
Romano Anna Maria	Casarano (LE)
Rossi Ernesto	Benevento
Rossi Mauro	Grosseto
Ruggeri Patrizia	Cremona
Russo Alfio	Catania
Saglietti Giuseppe	Omegna
Saitta Giovanni	Messina
Sanicandi Maurizio	Palmanova UD
Santini Costanza	Cesena
Savino Teresa	Bari
Sciangula Luigi	Como
Scurini Carmen	Napoli
Secchi Elio	Ozieri (SS)
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Serra Alberto	Anzio (RM)
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Serviddio Gaetano	Foggia
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Stagno Gaudenzio	Reggio Calabria
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Strazzabosco Marco	Vicenza
Stroppiana Mauro	Asti
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Velussi Mario	Aurisina (TS)
Vero Raffaella	Catanzaro
Vettor Roberto	Padova
Vinci Carmela	Venezia
Zavaroni Donatella	Piacenza
Zavaroni Ivana	Parma
Zenari Luciano	Negrar
Zenoni Luca	Seriate (BG)
Zucchi Pilade	Asola (MN)

micro- and macrovascular complications already have occurred. The use of insulin detemir at a relatively low dose, at least if compared to that used in RCTs, promotes a clinically relevant reduction of HbA_{1c} and fasting blood glucose levels, with a very low impact on hypoglycaemia risk and weight increase.

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